

# Role of Breast Milk Secretory Immunoglobulin A in Infants from 7–12 Months of Age with Acute Gastroenteritis

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## Abstract

**Objective:** Acute gastroenteritis is particularly dangerous during the first year of life due to an increased risk of water and electrolyte loss, which can lead to moderate to severe dehydration. This risk is especially high in infants who are not exclusively breastfed or are fed formula or commercial cow's milk. Human milk is not only a source of energy but also a complex, dynamic biological fluid with protective and immunomodulatory roles, serving as a bridge between the mother's immune system and the infant. Secretory immunoglobulin A is the first line of defense of the intestinal epithelium against pathogenic microorganisms. The aim of this study was to determine whether secretory immunoglobulin A from breast milk has a protective effect on the intestinal epithelium and whether it influences the severity of clinical picture and the duration of symptoms of acute gastroenteritis, depending on the infant's type of nutrition.

**Methods:** A total of 35 infants with acute gastroenteritis were divided into two groups based on feeding patterns (type of milk and non-milk food). Indicators evaluated included symptom severity, the need for parenteral rehydration, and the degree of dehydration.

**Results:** We found a statistically significant association between group affiliation and the sIgA test results between the first and second groups ( $P = 0.004933$ ), as well as in the average value of sIgA in stool ( $P = 0.000788$ ). Rotavirus was the most common cause of acute gastroenteritis.

**Conclusion:** The presence of breast milk sIgA in infants appears to influence the severity of acute gastroenteritis by reducing vomiting frequency, the number and severity of diarrheal episodes, the risk of moderate and severe dehydration, and the incidence of fever.

**Keywords:** Acute gastroenteritis, infants, sIgA, breast milk

## Introduction

Acute gastroenteritis is a leading cause of morbidity and mortality in developing and underdeveloped countries, where malnutrition and poor local healthcare systems contribute significantly to the severity of the clinical presentation.<sup>1</sup> It is particularly dangerous during the first year of life due to an increased risk of water and electrolyte loss, which can result in moderate to severe dehydration—especially in infants who are not exclusively breastfed or are fed with formula or commercial cow's milk. Viruses are the most common cause of acute gastroenteritis, with Rotavirus being predominant globally. However, Norovirus has become the leading cause in European countries and the United States, where rotavirus vaccination coverage is high. Infection of enterocytes leads to cell death, extrusion into the lumen, and atrophy of intestinal villi. This process reduces the intestinal surface area with disturbance of digestive and absorptive functions.

The health benefits of breastfeeding are more pronounced in developing countries than in developed ones. In developing regions, the most common causes of death in the first six months of life are diarrhea (55%) and lower respiratory infections (53%). In the second six months, these rates decrease to 20% and 18%, respectively.<sup>2</sup> Infants receive systemic protection transplacentally and local intestinal protection via colostrum and mature milk. Evidence supporting the protective role of breastfeeding against infectious disease-related infant mortality is strong, as demonstrated in a controlled study by Victora et al.<sup>3</sup> That study showed that bottle-fed infants had a 14.2-fold greater risk of death from diarrhea and a 3.6-fold greater risk from respiratory infections.

Human milk is not only a source of energy but also a complex, dynamic biological fluid with protective and

immunomodulatory functions. It serves as a critical link between the mother's immune system and the infant.<sup>4</sup> The immunological properties of human milk cannot be replicated in formula milk.<sup>4</sup> Breast milk contains a variety of immune components, including immunoglobulins, leukocytes, oligosaccharides, lysozyme, lactoferrin, IFN- $\gamma$ , nucleotides, and cytokines. Some of these components offer passive protection in both the gastrointestinal and upper respiratory tracts by preventing pathogen adherence to mucosal surfaces, thereby protecting the infant from invasive infections.<sup>5</sup> Although infants receive maternal antibodies transplacentally, they remain unprotected when they come into contact with new microorganisms.<sup>4</sup> Breast milk helps reduce this vulnerability by supplying additional antibodies that influence the infant's immune, metabolic, and microbial systems.<sup>4</sup>

sIgA is almost absent in newborns and infants, but is present in high concentrations in colostrum ( $\approx 10$  g/l) and mature milk ( $\approx 1$  g/l). The enteromammary circulation allows the mother's mucosal immune system to protect the infant's gut through human milk. When a pathogen enters the mother's gut, it is taken up by Peyer's patches and antigens are presented to lymphocytes. IgA production is induced on the basolateral side of the mammary cell, and IgA travels through the mammary cell to enter the milk as sIgA. sIgA through breast milk enters the gut of infants where it protects them by binding to the pathogen.

sIgA is almost absent in newborns and young infants but is present in high concentrations in colostrum ( $\approx 10$  g/l) and in mature milk ( $\approx 1$  g/l).<sup>6</sup> The enteromammary circulation allows the the maternal mucosal immune system to protect the infant's gut via breast milk. When a pathogen enters the mother's gastrointestinal tract, it is taken up by Peyer's patches

and its antigens are presented to lymphocytes. IgA is then produced at the basolateral side of mammary epithelial cells and IgA travels through the mammary cell to enter the milk as sIgA. Once ingested, this sIgA binds to pathogens in the infant's gut, providing protection.<sup>7</sup>

The essential role of mucus in intestinal immunity has been demonstrated by the discovery that the dense inner mucus layer is devoid of bacteria.<sup>8</sup> A study by Rogier et al. found that sIgA is absent from this inner layer but is associated with intestinal bacteria microflora in the outer mucosal layer.<sup>9</sup>

Although the mucosal immune system in newborns is immature, it contains all the necessary cellular components. The number of immunocytes in the intestinal lamina propria and salivary glands that produce IgA and IgM begins to increase 2–4 weeks after birth. It takes 1–2 years to reach adult levels of IgA plasma cells in the mucosa. sIgA prevents the attachment of antigens and pathogenic microorganisms to epithelial receptors by binding to the Fc receptors on pathogens, which can trigger antibody-dependent cell-mediated cytotoxicity. It also traps microorganisms in mucus and promotes their elimination through peristalsis and mucociliary action.<sup>10,11</sup> Natural and specific sIgA antibodies in breast milk can bind to commensal bacteria and may contribute to the development of the infant's intestinal microbiota. This, in turn, stimulates the maturation of intestinal lymphatic tissue and the production of IgA, which has limited affinity for recognition and removal of pathogenic microorganisms.<sup>10</sup>

## Materials and Methods

### Study Design

This prospective cohort study included infants aged 7–12 months who were diagnosed with acute gastroenteritis. All infants were hospitalized at the Children's Department of Clinical Hospital – Stip. Written consent was obtained from the parents of each infant included in the study. A survey questionnaire was designed, and responses were obtained from the infants' mothers. The questionnaire covered the following details: infant age, type of nutrition (breast milk, formula, or other types of milk), and weaning practices. It also included information on the onset of acute gastroenteritis symptoms within 24 hours prior to admission, as well as data on the diet and health status of the nursing mother. Infants were divided into two groups according to their type of milk nutrition and the introduction of complementary food:

Group I included infants aged 7–12 months who were breastfed and additionally received other types of milk and complementary feeding.

Group II included infants aged 7–12 months who were fed with formula or other types of milk, along with complementary feeding.

The clinical presentation and degree of dehydration were assessed through physical examination. Dehydration was classified as mild, moderate, or severe using a clinical scoring system based on the World Health Organization's *Integrated Management of Childhood Illness – Module 4: Diarrhea*. For each infant, a record sheet was completed, and based on the severity of clinical signs, the need for parenteral rehydration during hospitalization was evaluated. Infants with diarrhea due to surgical or extra-intestinal causes, as well as those who had received immunosuppressive therapy, were excluded from

the study. This study was approved by the Clinical Research Ethics Committee of Clinical Hospital – Stip (Approval No. 03/1534/1).

### Laboratory Methods

From each infant included in the study, two stool samples were collected from diapers. One sample was placed in a sterile plastic container labeled with the patient's general information and the code. Within 30 minutes of collection, it was transported to the Microbiological Laboratory at the Center for Public Health – Stip. This first sample was tested for the presence of Rotavirus and Adenovirus using an immunochromatographic test (DUO ROTA-ADENOVIRUS-Check-1, VEDA. LAB, Alençon, France). A coproculture was also performed on the same sample by sowing the stool sample on a suitable substrate to rule out the presence of enteropathogenic bacteria. The second stool sample was used to quantitatively determine the sIgA level using the ELISA method with a commercial ELISA kit (Immundiagnostik, Bensheim, Germany).

### Statistical Methods

The collected data were processed using the statistical program SPSS 20 and the following statistical methods: Attributive statistical series were analyzed by determining percentages, Numerical series were analyzed with central tendency measures and data dispersion measures, Statistical significance of the probability between numerical series was determined using Student's *t*-test, Correlative relationships were realized with the assistance of Pearson's linear correlation coefficient, the probability of association between two frequency distributions attributive variables were assessed with the Pearson Chi square test and Fisher exact 2 tailed test. Statistical significance was defined as  $P < 0.05$ . Results are presented in tables and figures.

## Results

The analysis included 35 hospitalized infants aged 7–12 months with a diagnosis of acute gastroenteritis, divided into two groups. The first group included 19 (54.3%) infants and the second group included 16 (45.7%) infants, divided by age expressed in months and type of nutrition. Table 1 presents the infants with acute gastroenteritis by gender and sex.

The average infant age in the first group was  $9.3 \pm 1.2$  months and in the second group was  $9.5 \pm 1.4$  months. The distribution of the clinical signs in both groups is presented in Table 2, which includes the average number of vomiting, average number of liquid stools, fever, degree of dehydration, number of days of parenteral rehydration, and length

Table 1. Distribution of the infants according to the gender and age

Group	I		II	
Gender	Number	%	Number	%
Male	11	57.9%	6	37.5
Female	8	42.1%	10	62.5
Age in months	Number	Mean! SD	Number	Mean! SD
	19	9.3! 1.249561	16	9.5! 1.366260

SD: Standard deviation.

of hospital stay. The average number of vomiting prior to admission among infants in the first group was  $2.7 \pm 3.3$ , in the second group  $4.6 \pm 3.3$ , the difference was statistically insignificant for  $P > 0.05$  ( $t = -1.62537$ ,  $P = 0.113598$ ). The average number of liquid stools prior to admission among infants in the first group was  $5.9 \pm 2.4$ , in the second group  $9.0 \pm 4.2$ , the difference was statistically significant for  $P < 0.05$  ( $t = -2.67615$ ,  $P = 0.011505$ ). Fever was reported in 26.3% of infants in the first group and in 68.75% in the second group. The percentage difference was statistically significant for  $P < 0.05$  (Difference test,  $P = 0.0120$ ). In the first group, a mild degree of dehydration was registered in 78.9% of infants, and moderate in 21.1%. In the second group, a mild degree of dehydration was registered in 18.75%, a moderate degree in 62.5% and a severe degree of dehydration in 18.75%. The percentage difference is statistically significant for  $P < 0.05$  ( $P = 0.0004$  - mild grade I vs II group;  $P = 0.0128$  - moderate grade I vs II group). The average number of liquid stools during the treatment in the first group was  $14.1 \pm 7.9$ , and in the second group it was  $18.6 \pm 10.3$ , the difference between the average number of liquid stools was statistically insignificant for  $P > 0.05$  ( $P = 0.152484$ ). The average number of vomiting during treatment in the first group was  $1.4 \pm 1.9$ , and in the second group it was  $3.4 \pm 3.0$ , the difference between the average number of vomiting was statistically significant for  $P < 0.05$  ( $P = 0.025661$ ). The average number of days of parenteral rehydration in the first group was  $1.7 \pm 1.2$ , and in the second group it was  $2.1 \pm 1.1$ , the difference between the average number of days of parenteral rehydration was statistically insignificant for  $P > 0.05$  ( $P = 0.336684$ ). The average number of days of hospitalization in the first group was  $3.9 \pm 1.6$ , and in the second group it was  $4.9 \pm 1.4$ , the difference between the average number of days of hospitalization was statistically insignificant for  $P > 0.05$  ( $P = 0.054966$ ).

Rotavirus was positive in 14 stool samples. In the first group, Rotavirus was positive in 6 (31.6%) infants, and in the second group, Rotavirus was positive in 8 infants (50%). Adenovirus was isolated in one infant from the second group. Salmonella enteritidis was isolated in two infants from the second group and Proteus mirabilis was isolated in one infant from the same group (Figure 1).

The average value of sIgA in infants diagnosed with acute gastroenteritis in the first group was  $4422.5 \pm 3208.7$  ug/ml, and in the second group it was  $1286.5 \pm 1180.6$  ug/ml, the difference between the average value is statistically significant for  $P < 0.05$  ( $P = 0.000788$ ) (Figure 2).

Table 3 shows the effect of sIgA on the degree of dehydration, vomiting symptom and fever in infants with acute gastroenteritis. We found a statistically significant association between dehydration rate, and fever frequency between the first and second group.

## Discussion

The immune system of infants develops significantly in the first 2 years of life. However, infants have limited abilities to respond quickly and effectively to infectious challenges, which explains the susceptibility of infants to infections.<sup>5</sup> Frank et al.

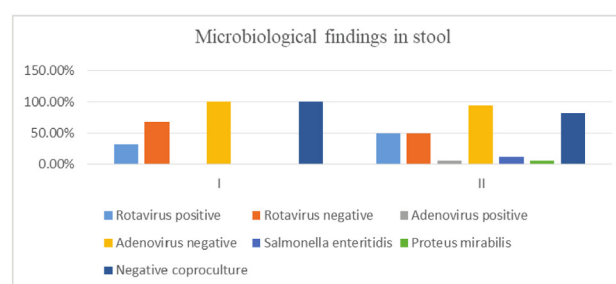


Fig. 1 Microbiological findings in stool.

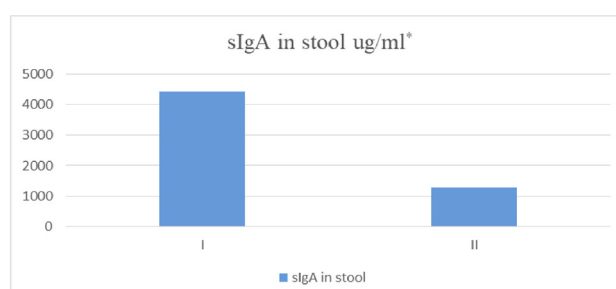


Fig. 2 Average value of sIgA in infants with acute gastroenteritis. sIgA: secretory Immunoglobulin A,  $t$ -test = 3,697013;  $P = 0,000788$  (statistically significant).

Table 2. Clinical condition 24 hours before admission and during the hospitalization

Group	Average	Average	<i>t</i> -test	<i>P</i>	N		SD	
	I	II			I	II	I	II
Number of vomiting 24 hours before admission	2.736842	4.562500	-1.62537	0.113598	19	16	3.280280	3.346018
Number of stools 24 hours before admission	5.9	9.0	-2.67615	0.011505	19	16	2.391505	4.242641
Number of stools during the hospitalization	14.1	18.6	-1.46463	0.152484	19	16	1.865350	3.03040
Number of vomiting during the hospitalization	1.4	3.4	-2.33692	0.025661	19	16	1.865350	3.03040
Number of parenteral rehydration days	1.7	2.1	-0.97494	0.336684	19	16	1.240166	1.08781
Number of hospitalization days	3.9	4.9	-1.98968	0.054966	19	16	1.629408	1.43614

SD: Standard deviation; N: Number.

Table 3. Effect of sIgA on the clinical condition in infants with acute gastroenteritis

	Negative sIgA	Positive sIgA	P
<b>Dehydration degree</b>	<b>N = 6</b>	<b>N = 29</b>	
Mild	0	17 (58.6%)	$P = 0.019061$
Moderate	5 (83.3%)	10 (34.5%)	
Severe	1 (16.7%)	2 (6.9%)	
<b>Fever</b>	<b>N = 6</b>	<b>N = 29</b>	
No	1 (16.7%)	18 (62.1%)	$P = 0.042141$
Yes	5 (83.3%)	11 (37.9%)	
<b>Vomiting</b>	<b>N = 6</b>	<b>N = 29</b>	
No	2 (33.3%)	13 (44.8%)	$P = 0.604542$
Yes	4 (67.3%)	16 (55.2%)	

N: Number; sIgA: secretory Immunoglobulin A.

found that breastfeeding was inversely associated with the incidence of respiratory infections with fever, otitis media, and infectious gastroenteritis.<sup>12</sup> Santos et al. observed that children who were exclusively breastfed until 6 months of age and whose breastfeeding was continued until 12 months of age had a lower rate of hospitalizations due to diarrhea and it was concluded that breastfeeding is a significant factor in the prevention and protection of diarrhea in children under two years of age.<sup>13</sup> Diallo et al. found that cessation of breastfeeding before three and six months of age was significantly associated with a high incidence of diarrhea at 6 months of age and between 6 and 12 months of age. Formula feeding for  $\geq 3$  months was associated with more frequent diarrhea between 6 and 12 months of age.<sup>14</sup> Lamberti et al. evaluated the level of suboptimal breastfeeding as a risk factor for morbidity and mortality from diarrhea. Infants who were not breastfed, had an extremely high risk of mortality from diarrhea compared to those who were exclusively breastfed.<sup>15</sup> Ladomenou et al. observed that prolonged exclusive breastfeeding was associated with fewer infectious episodes and fewer admissions to hospital for infection in the first year of life. Partial breastfeeding did not have that protective effect.<sup>16</sup> Studies have confirmed that breastfed infants had significantly higher concentrations of sIgA in their stools compared to those formula fed, suggesting that breast milk provides large amounts of sIgA to infants.<sup>17,18</sup> In the first group of this study, sIgA was positive in all infants, while in the second group sIgA was positive in 37.5%. A statistically significant association was recorded between group affiliation and sIgA test for  $P < 0.05$  ( $P = 0.004933$ ). Studies found that breastfeeding may not have an impact on the occurrence of rotavirus acute gastroenteritis, but it does have an impact on reducing the severity of the clinical presentation in breastfed infants.<sup>19,20</sup> In our study, rotavirus was positive in 14 stool samples. Rotavirus was positive in 6 infants in the first group, and in 8 infants in the fourth group. The adenovirus test was positive in one infant in the second group. The stool culture was negative in the first group. In the second group, Salmonella enteritidis was detected in two infants and Proteus mirabilis was detected in one infant. In study by Sherif et al. were examined the effects of stool sIgA on the clinical presentation of rotavirus acute gastroenteritis in infants and the majority of breastfed infants had positive stool sIgA values compared to those formula fed.

Those who were positive for sIgA in stool had a milder clinical picture, with a mild dehydration degree, a lower vomiting frequency, and the number of infants with fever was lower.<sup>21</sup> In this study, we assessed the clinical presentation of infants with acute gastroenteritis on admission, taking into account clinical signs and symptoms 24 hours prior to hospital admission and assessing the clinical condition during treatment itself, the need for parenteral rehydration, and the length of hospitalization. No statistically significant difference was observed for the average number of vomiting episodes before admission between the first and second group. For the number of liquid stools 24 hours before admission, a statistically significant difference was registered between the first and second group, with a lower average number of liquid stools in the first group compared to the second group ( $P < 0.05$ ,  $P = 0.011505$ ). The percentage difference in the number of infants with fever was statistically significant between the first and second group (26.3% vs 68.75),  $P < 0.05$ ,  $P = 0.0120$ . In this study, it was observed that mild dehydration was more prevalent in the first group, while severe dehydration was more prevalent in the second group. The percentage difference was statistically significant at  $P < 0.05$  ( $P = 0.0004$  – mild dehydration group one versus group two;  $P = 0.0128$  – moderate dehydration group one versus group two). A significantly lower degree of dehydration (moderate and severe) was registered in sIgA positive patients ( $P < 0.05$ ,  $P = 0.019061$ ) between first and the second group. Similar results were obtained in the study by Fuchs et al. which examined the association between the occurrence and severity of dehydration in infants with diarrhea according to the age of the infants, the type of milk consumed, the time since cessation of breastfeeding, and the breastfeeding status.<sup>22</sup> In infants younger than 12 months, the risk of developing diarrhea was highest during the first 9 months of life, especially in the first 2–3 months (OR = 7.1) ( $P = 0.001$ ). Infants who were not breastfed faced a higher risk of dehydration than those who were exclusively breastfed ( $P = 0.006$ ). Infants who consumed only cow's milk or only formula faced the highest risk of developing dehydration (OR = 6 and 6.9; respectively). Infants who were not exclusively breastfed had an intermediate risk of developing dehydration (OR = 1.3–2.2). Infants who stopped breastfeeding had a high risk of developing dehydration (OR = 6.4) ( $P = 0.001$ ). This risk was particularly high in the first 2 months after stopping breastfeeding (OR = 8.4), and then decreased.<sup>22</sup> During treatment, vomiting was less frequent in infants in the first group compared to the second group, with a statistically significant difference between the mean number of vomiting episodes at  $P < 0.05$ . In the study by Weinberg et al. a difference was observed between the groups for the frequency of vomiting, which was significantly lower in infants fed with breast milk.<sup>23</sup> No statistically significant difference was observed between the first and second group for the average number of stools during treatment, the number of days for parenteral rehydration, and the number of days of hospitalization. Studies have shown that the presence and levels of specific sIgA antibodies in breast milk are not constant throughout lactation, suggesting that the protective role varies at certain periods of lactation, and this may also have an impact on the severity of the clinical picture.<sup>24,25</sup>

The finding that breastfed infants had significantly higher sIgA levels and milder clinical courses supports targeted public health messaging and breastfeeding advocacy in managing infant diarrheal disease. This study supports the concept



of enteromammary immunity - the transfer of maternal immune information to the infant through breast milk - by linking the presence of sIgA in stool to clinical outcomes. It reinforces that exclusive and continued breastfeeding can mitigate not just the incidence, but also the severity of diarrheal episodes. This study had limitations due to the small number of patients. This is likely due to the reduction in the incidence of diarrhea in infancy, especially diarrhea caused by rotavirus, due to the introduction of mandatory rotavirus vaccine in the immunization schedule in our country. During research of the published literature, we revealed a small number of studies examining the direct effect of breast milk sIgA on the severity of the clinical picture in infants with acute gastroenteritis. For getting more significant evidence-based conclusions, more studies such as this one, higher number of participants and follow-up over a longer period of time are necessary.

## Conclusion

Although our study was limited by the small number of patients, we have shown that the presence of breast milk sIgA

in infants has an effect on the severity of the clinical picture of acute gastroenteritis by reducing the frequency of vomiting, the number and severity of diarrheal episodes, the risk of moderate and severe dehydration, and fever frequency. It takes 2 years to reach adult levels of secretory IgA in the intestinal mucosa and that is the reason why breastfeeding is so important, especially in the first two years of a child's life. Hence, mothers should be encouraged to breastfeed their children, because breast milk provides high concentrations of sIgA, which protects the intestinal epithelium of infants from damage in the presence of enteric pathogens.

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## Conflicts of Interest Disclosure

Authors declare no conflict of interest. ■

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